Message

From: Paul-Friedman, Katie [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=9DE6209426A941908301318615F5507B-PAUL-FRIEDM]
Sent: 7/9/2019 12:38:35 PM
To: Pham, Nathalie@OEHHA [Nathalie.Pham@oehha.ca.gov]
Subject: RE: Cytotoxicity cutoff for ToxCast/Tox21 data
Attachments: invitrodb_v3_2_burst_assays_values_8jul2019.xlsx

Hi Nathalie,

Apologies for the delay, I've just been really swamped plus the holiday. You've been on my list.

I've tried to answer in text below and also attached a spreadsheet that I think should help.

Please email me again if you have any more questions or something I've said here doesn't make sense.

Best,
Katie

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From: Pham, Nathalie@OEHHA <Nathalie.Pham@oehha.ca.gov>
Sent: Monday, July 8, 2019 7:09 PM
To: Paul-Friedman, Katie <Paul-Friedman.Katie@epa.gov>
Subject: RE: Cytotoxicity cutoff for ToxCast/Tox21 data

Hi Katie –
I reached out last week, but did not hear back so just wanted to check in. See my questions below. Thank you for all your help.

Nathalie

From: Pham, Nathalie@OEHHA
Sent: Tuesday, July 2, 2019 4:08 PM
To: Paul-Friedman, Katie <Paul-Friedman.Katie@epa.gov>
Cc: Sun, Meng@OEHHA <meng.sun@oehha.ca.gov>
Subject: RE: Cytotoxicity cutoff for ToxCast/Tox21 data

Hi Katie –

It is a pleasure to e-meet you. Thank you for the clarification on the cytotoxicity threshold currently on the dashboard. I had a couple of follow-up questions per your earlier email that I was hoping you could answer –

- Do you know which chemicals have been screened through all 88 assays or how we could find that information? Is there a list of the 88 assays or would we just look at individual assay design/biological process target?

The cytotox table for any release of invitrodb (current release is version 3.1, but version 3.2 is coming soon) is available for download as a summary file here:
ftp://newftp.epa.gov/comptox/High_Throughput_Screening_Data/InVitroDB_V3.1/Summary_Files/

You can find this information using the database (burst=1 in the assay_component_endpoint table), but likely using the Dashboard will be an inefficient way to answer this question. Do you have an instance of invitrodb running, or are you relying on the Dashboard? I am happy to use the database to help you if the Dashboard is not sufficient – and in this case, it would be difficult to get to this answer as the Dashboard is entered by chemical or target, at least in the current version. The summary file would be the best bet. However, we are about to release invitrodb v3.2 (August 2019). So I've attached a spreadsheet with two tabs for invitrodb version 3.2 in advance of our release. One tab is the 88 "burst" or cytotoxicity assays from the assay_component_endpoint table of the database that are currently used in the cytotoxicity threshold calculation. If you use this information, you can cite invitrodb v3.2. This should be given a DOI imminently. The DOI for the previous version, invitrodbv3.1 is: https://doi.org/10.23645/epacomptox.6062623.v3. Please note that not all chemicals are tested in all 88 assays. The data table has the following features using the function tcplCytoPt() from our tcpl R package.

The resulting data.table has the following fields:

1. *"chid" – The chemical ID.*
2. *"code" – The chemical code.*
3. *"chnm" – The chemical name.*
4. *"casn" – The chemical CASRN.*
5. *"med" – The median of the "burst" endpoint log(AC50) ("modl_ga" in the level 5 output) values.*
6. *"mad" – The MAD of the "burst" endpoint log(AC50) values.*
7. *"ntst" – The number of "burst" endpoints tested.*
8. *"nhit" – The number of active "burst" endpoints.*
9. *"use_global_mad" – TRUE/FALSE, whether the mad value was used in the global MAD calculation.*
10. *"global_mad" – The median of the "mad" values where "use_global_mad" is TRUE.*
11. *"cyto_pt" – The cytotoxicity point, or the value in "med" when "nhit" is at least 2.*
12. *"cyto_pt_um" – 10^cyto_pt*
13. *"lower_bnd_um" – 10^(cyto_pt - 3*global_mad)*

- In the past, I remember there was material stating 3 MADs from the cytotoxicity limit was a good rule of thumb for specificity of an assay hit. Is that still an applicable rule?

The cytotoxicity limit in the dashboard (the line shown) is already the lower bound, so you would not want to subtract 3MAD from that. More precisely, the lower bound is the cyto_pt -3(global MAD). The global MAD calculation is based on only the chemicals that have been screened in all of the current 88 assay endpoints considered for the cytotox burst calculation and have a hit in at least 5% of these 88 assay endpoints. Further, if a chemical is a hit in less than 5% of the 88 associated assay endpoints, we have assigned a default value of 1000 micromolar.*

Thanks Katie,

Nathalie

From: Sun, Meng@OEHHA <meng.sun@oehha.ca.gov>
Sent: Tuesday, July 2, 2019 9:27 AM
To: Paul-Friedman, Katie <Paul-Friedman.Katie@epa.gov>; Williams, Antony <Williams.Antony@epa.gov>

Cc: Pham, Nathalie@OEHHA <Nathalie.Pham@oehha.ca.gov>
Subject: RE: Cytotoxicity cutoff for ToxCast/Tox21 data

Hi Katie and Tony,

Thank you both very much for the publication and explanation. Now we have a better understanding for the cytotoxicity threshold. I'd like to introduce my colleague Nathalie Pham. She also uses ToxCast data frequently and may reach out to you for technical questions. We really appreciate your help with our use of the Chemicals Dashboard.

Best,
Meng

From: Paul-Friedman, Katie <Paul-Friedman.Katie@epa.gov>
Sent: Monday, July 1, 2019 6:32 PM
To: Williams, Antony <Williams.Antony@epa.gov>; Sun, Meng@OEHHA <meng.sun@oehha.ca.gov>
Subject: RE: Cytotoxicity cutoff for ToxCast/Tox21 data

Hi Meng and Tony,

Yes, the publication that Tony referenced provides a detailed description of the calculation. Currently there are 88 cytotoxicity assays that can be included in the cytotoxicity threshold computation (though not all chemicals have been screened in all 88). The cytotoxicity threshold that appears on the Dashboard is actually the lower bound on the prediction of the median cytotoxicity, so it will appear lower than many of the hits. We do not currently filter out any data; the cytotoxicity threshold is truly more for context in terms of identifying activity that looks like it occurs "specifically," i.e. less likely to be confounded by cytotoxicity. Obviously any filtering applied by a user should be context specific. I'm happy to dive deeper into this and the computation itself with you if you have some more specific questions. Please reach out anytime.

Kind regards,
Katie

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From: Williams, Antony
Sent: Monday, July 1, 2019 8:39 PM
To: Sun, Meng@OEHHA <meng.sun@oehha.ca.gov>
Cc: Paul-Friedman, Katie <Paul-Friedman.Katie@epa.gov>
Subject: RE: Cytotoxicity cutoff for ToxCast/Tox21 data

Meng,

Thank you for your email. While I can take a poke at a number of your questions I believe that the publication at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6280881/ will cover a number of your questions. My colleague Katie Paul-Friedman is far more familiar with the data and details of determining the cytotoxicity limits and I have cc'ed her on this email as her responses will offer way more detail than I can provide. Best wishes.

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Try out the CompTox Chemicals Dashboard and access data for almost 875,000 chemical substances

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From: Sun, Meng@OEHHA <meng.sun@oehha.ca.gov>
Sent: Monday, July 1, 2019 2:07 PM
To: Williams, Antony <Williams.Antony@epa.gov>
Subject: Cytotoxicity cutoff for ToxCast/Tox21 data

Hi Tony,

I hope you are doing well. This is Meng from OEHHA at Cal/EPA. My colleagues and I have some additional questions regarding the Chemicals Dashboard. It is such a great resource and we are trying to make the best use out of it.

Our questions are: how do you calculate the single cytotoxicity cutoff that appears on the "chemical activity summary" chart? Is it based on a combination of the variability assay results? Do you use this cutoff to filter out any assays? For example, the cytotoxicity cutoff for 4-aminophenol is very low (8.22 µM) and a lot of the current "positives" have an AC50 of higher than 20 or even 50 µM. When we checked individual variability assays, the AC50s look more comparable to the AC50s of the "real signal" such as ER inhibition. We are trying to tease out the cytotoxic effect from specific receptor antagonism, and wonder if we can use this cutoff or should check individually paired variability assay results.

Thank you very much!

Meng

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